Efficacy and Safety of Zanubrutinib in Japanese Patients With Mature B-Cell Malignancies

Authors: Takayuki Ishikawa,[1] Masahiro Takeuchi,[2] Kazuyuki Shimada,[3] Kohmei Kubo,[4] Takeshi Kondo,[5] Katsuya Fujimoto,[6] Tomoaki Fujisaki,[7] Koji Nagafuji,[8] Rika Sakai,[9] Shingo Kurahashi,[10] Tatsuro Jo,[11] Kazutaka Sunami,[12] Senji Kasahara,[13,14] Tomonori Nakazato,[15] Haiyi Guo,[16] William Novotny,[16] Chris Tankersley,[16] Motohisa Takai,[16] Hui Yao,[16] Jinhua Zhong,[16] Hongjie Zhu,[16] and Koji Izutsu[17]

Affiliations: [1]Kobe City Medical Center General Hospital, Kobe, Japan; [2]Chiba Cancer Center, Chiba, Japan; [3]Nagoya University Hospital, Nagoya, Japan; [4]Aomori Prefectural Central Hospital, Aomori, Japan; [5]Aiiku Hospital, Sapporo, Japan; [6]National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan; [7]Matsuyama Red Cross Hospital, Matsuyama, Japan; [8]Kurume University Hospital, Kurume, Japan; [9]Kanagawa Cancer Center, Yokohama, Japan; [10]Toyohashi Municipal Hospital, Toyohashi, Japan; [11]Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan; [12]National Hospital Organization Okayama Medical Center, Okayama, Japan; [13]Gifu Municipal Hospital, Gifu, Japan; [14]Gifu Pharmaceutical University, Gifu, Japan; [15]Yokohama Municipal Citizen's Hospital, Yokohama, Japan; [16]BeiGene (Shanghai) Co., Ltd., Shanghai, China and BeiGene USA, Inc., San Mateo, CA, USA; and [17]National Cancer Center Hospital, Tokyo, Japan

Background/Introduction: Zanubrutinib is a potent, irreversible Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize off-target kinase inhibition. Zanubrutinib is approved globally for the treatment of B-cell malignancies in adults. Here, we present the efficacy and safety of zanubrutinib assessed in patients with mature B-cell malignancies enrolled in the ongoing, multicenter, open-label phase 1/2 study in Japan (BGB-3111-111; NCT04172246).

Methods: In part 1, safety and tolerability of zanubrutinib were evaluated in 6 enrolled patients with mature B-cell malignancies who received zanubrutinib 160 mg orally twice daily. In part 2, the safety and efficacy of zanubrutinib were evaluated in 47 enrolled patients with relapsed/refractory (RR) mantle cell lymphoma (MCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and Waldenström macroglobulinemia (WM). Responses were assessed by investigators based on the Lugano Classification for MCL and SLL, 2018 International Workshop on CLL (iwCLL) guidelines with modification for treatment-related lymphocytosis for CLL, and WM response criteria updated at the 6th International Workshop on WM.

Results: As of May 10, 2022, 53 patients have been enrolled (12 RR MCL; 17 CLL/SLL; 21 WM; 2 follicular lymphoma; 1 marginal zone lymphoma). Fourteen (26.4%) patients discontinued treatment (9 progressive disease, 2 adverse event [AE], 2 investigator decision, 1 withdrawal by patient). The median age was 71 years (range, 37-84) and 67.9% were men. RR patients (49.1%) received a median of 2 lines of prior therapy (range, 1-8). The median follow-up time was 14.8 months (range, 1.4-27.3). Forty-eight (90.6%) patients experienced ≥1 treatment-emergent adverse event (TEAE). The most common any-grade AEs are summarized in **Table 1**. Twenty-two (41.5%) patients experienced grade ≥3 AEs; the most common grade ≥3 AEs were neutrophil count decreased (9.4%), platelet count decreased (9.4%), and neutropenia (5.7%). One patient with RR MCL experienced a fatal TEAE of septic shock. Thirty-five (66%) patients had ≥1 TEAE of special interest, including 21 (39.6%) patients with hemorrhage, 17 (32.1%) with infections, and 11 (20.8%) with thrombocytopenia. The most common grade ≥3 TEAEs of special interest were neutropenia (15.1%), infections (11.3%), hemorrhage (9.4%), and thrombocytopenia (9.4%). Investigator-assessed disease responses are reported from part 2. Among patients with MCL, the overall response rate (ORR) was 81.8%. Among patients with CLL/SLL, the ORR (partial response with lymphocytosis or better) was 92.9% in treatment-naïve (TN) patients and 100% in RR patients. The ORR among patients with WM was 92.3%, including 15.4% very good partial response (VGPR) in TN

patients, and 100%, including 66.7% VGPR, in RR patients (**Table 2**). The median duration of overall response has not been reached for any disease cohort.

Conclusion: Preliminary data from this phase 1/2 study demonstrate that zanubrutinib can be an efficacious and safe BTK inhibitor for Japanese patients with RR MCL, CLL/SLL, and WM. Safety and efficacy data are comparable with those observed in published data across ethnic groups.

Table 1: Adverse Events

AEs, n (%)	**Total N=53**
Any AE	48 (90.6)
Any grade ≥3 AE	22 (41.5)
Serious AEs	13 (24.5)
Fatal AEs	1 (1.9)
AEs leading to dose interruption	14 (26.4)
AEs leading to dose reduction	2 (3.8)
AEs leading to treatment discontinuation	2 (3.8)
Most frequent AEs (≥4 patients any grade)	
Platelet count decreased	10 (18.9)
Pyrexia	7 (13.2)
Neutrophil count decreased	6 (11.3)
Anemia	5 (9.4)
Back pain	5 (9.4)
Constipation	5 (9.4)
Decreased appetite	5 (9.4)
Hypertension	5 (9.4)
Purpura	5 (9.4)
Arthralgia	4 (7.5)
Headache	4 (7.5)

AE, adverse event.

Table 2: Investigator-Assessed Overall Response

	MCL	CLL/SLL		WM	
	RR (n=11)	TN (n=14)	RR (n=3)	TN (n=13)	RR (n=6)
Median follow-up of response assessment, months (range)	11.0 (1.4-16.7)	11.2 (5.6-16.6)	16.6 (5.3-16.6)	11.1 (1.0-16.6)	11.1 (0.9-16.7)
ORR,[a] n (%) [95% CI]	9 (81.8) [48.2, 97.7]	13 (92.9) [66.1, 99.8]	3 (100) [29.2, 100.0]	12 (92.3) [64.0, 99.8]	6 (100) [54.1, 100.0]
CR	1 (9.1)	0	0	0	0
VGPR	-	-	-	2 (15.4)	4 (66.7)
PR	8 (72.7)	9 (64.3)	3 (100.0)	6 (46.2)	1 (16.7)
PR-L	-	4 (28.6)	0	-	-
MR	-	-	-	4 (30.8)	1 (16.7)
SD	0	1 (7.1)	0	0	0
PD	1 (9.1)	0	0	1 (7.7)	0
Discontinued before first assessment, n (%)	1 (9.1)	0	0	0	0

CLL, chronic lymphocytic leukemia; CR, complete response; MCL, mantle cell lymphoma; MR, minor response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; RR, relapsed or refractory; SD, stable disease; TN, treatment naïve; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

[a]The overall response rate is defined as PR or better for MCL; PR-L or better for CLL/SLL; MR or better for WM.